VOLUME-9, ISSUE-4, APRIL -2020 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Medicine

50 SHADES OF GREY: DOES SERUM PROCALCITONIN PREDICT ALL CAUSE MORTALITY IN PATIENTS WITH SEPSIS AND SEPTIC SHOCK?

Surg Cdr Manisha Thakur	Classified Specialist, INHS Kalyani, Gandhigram Post – 530005
Col KV Padmaprakash*	Senior Advisor (Medicine and Gastroenterology), INHS Kalyani, Gandhigram Post – 530005 *Corresponding Author
Surg Capt A Chauhan	Senior Advisor (Medicine), INHS Kalyani, Gandhigram Post – 530005
Lt Col Shashi Bhushan	Classified Specialist (Medicine), INHS Kalyani, Gandhigram Post – 530005
Surg Cdr Rahul Tyagi	Graded Specialist (Pulmonary Medicine), INHS Kalyani, Gandhigram Post – 530005
Surg Cdr Deep Kamal	Graded Specialist (Medicine), INHS Kalyani, Gandhigram Post – 530005
Surg Lt Cdr Prashant Jambunathang	Graded Specialist (Medicine), INHS Kalyani, Gandhigram Post – 530005

ABSTRACT **Background** The concept, definition and understanding of sepsis may have undergone several changes in the past years, but its omniscient nature in modern day critical care medicine has made accurate diagnosis, early initiation of therapy and relatively accurate prognostication, imperative. In recent times, procalcitonin has been used to initiate, de-escalate and guide antibiotic therapy. However, the data on its ability to predict all cause mortality in patients with sepsis remains nebulous. There is adequate evidence to merit considering both sides of the story. **Methods** We studied 99 consecutive patients meeting the diagnostic criteria for sepsis according to Sepsis 3 consensus criteria. Serum procalcitonin levels were compared head to head with 30-day all-cause mortality. Chi square paired and unpaired T and Pearson's coefficient were used to analyze the data. **Results** Our study showed that patients with a higher baseline value of serum procalcitonin had higher rate of in-hospital mortality (SD – 1.8 vs SD - 0.68, 2-tailed P<0.001). However, no statistically significant association was noted between baseline PCT and duration of ICU stay. **Conclusions** The predictive value of serum PCT, for mortality has been a matter of debate and controversy with compelling evidence to both sides of the story available in contemporary literature. Our study re-enforces the dictum of early diagnosis and treatment of sepsis in conjunction with the judicious use of serum procalcitonin. On the horizon, the authors see a plethora of newer biomarkers (SUPAR and sTREM-1) which may be used standalone or in combination to improve outcomes.

KEYWORDS : Sepsis, septic shock, Procalcitonin

INTRODUCTION

Sepsis is defined as a life threatening, dysregulated immune response to infection that results in organ dysfunction . Clinical features include signs of infection, altered mentation, hypotension and hepatic, renal or hematologic dysfunction. According to the Sepsis 3 criteria, this condition has been described as an acute increase in > 2 sepsis organ failure assessment points. Septic shock was defined as the need for vasopressors to maintain a mean arterial pressure to >65 mmHg, with a serum lactate concentration >2 mmol/L despite adequate fluid resuscitation . Sepsis can be both community and hospital acquired . Pneumonia is the most common source , with abdominal or genitourinary sources being the second and third most common. About one third patients would have a positive blood culture, thereby contributing to the enigma in diagnosis.

Patients with sepsis can have cardiorespiratory complications, neurologic and hematological sequalae, acute kidney injury and additional manifestations like adrenal crisis, sick euthyroid illness, dysfunction of hypothalamic-pituitary axis and DIC.

Procalcitonin is a serum biomarker that rises in bacterial infection and may therefore be of utility in prediction and prognostication in such infections . In healthy individuals, its synthesis is limited to thyroid neuroendocrine cells and therefore not detectable in normal individuals. In patients with infection, synthesis of procalcitonin is upregulated in nearly all tissues. Triggers for procalcitonin synthesis in infected individuals include TNF alpha, endotoxins, IL-1 and IL-6. Specific etiological agents associated with procalcitonin rise include Streptococcus pneumonia, Hemophilus influenzae, Pneumocystis jeroveci, Candida and Malaria are all known to cause significant elevations in procalcitonin.

Serum procalcitonin rises within 4 hours of an inflammatory stimulus and peaks at 24 to 48 hours . Peak levels corelate with severity of infection and levels of procalcitonin decline by 50% every day after resolution of infection. The rate of fall is less predictable in patients with renal dysfunction.

As on date, serum procalcitonin may be used for antibiotic initiation, discontinuation and prognostication in patients with sepsis. In this study we aim to corelate the levels of serum

procalcitonin with duration of ICU stay and mortality.

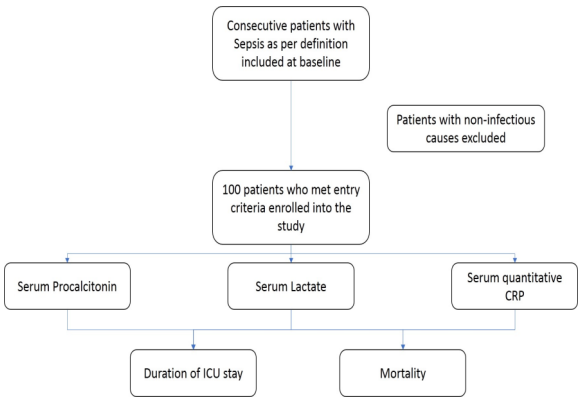
Methods

1. Study design and setting - This study was a single center prospective cross-sectional study carried out over a period of 18 months at a resource limited service hospital.

2. Study participants and inclusion criteria - 100 consecutive patients who were admitted to the hospital with signs of sepsis, defined by the Sepsis 3 consensus, as a qSOFA of 2 or more on admission. The patients were monitored for signs of progressive organ dysfunction and were managed according to existing standard of care. Each of these patients were subjected to investigations as detailed in Table 1.

3. Exclusion criteria – Patients with a known prior non-infectious cause, which could independently contribute to mortality were excluded. These include, but were not limited to autoimmune conditions (SLE, Sjogren's, Dermatomyositis), advanced cardiovascular disease (DCM with EF<20%), neutropenic patients and transplant patients.

4. Study design – The study design is detailed in Figure 1.



Additionally, other baseline and relevant investigations were carried out on all patients. As the patients were all managed according to existing standard of care, consent was waived. The data was analyzed and P value of < 0.05 was considered. Correlation co-efficient, Unpaired T test and Chi square test was used to analyze the data.

Results

The mean age of patients was 56.48 ± 13.85, with 31% females and the rest were males (Figure 1). The mean TLC was 18644 ± 3030.3. Other parameters are discussed in Table 2.

Table 2: Table of characteristics measured for primary outcome

Age (years)	56.48 ± 13.85
Gender (Male/Female)	69 % Male
TLC	18,644 ± 3030.92
CRP	83.649 ± 51.3
Procalcitonin	1.29 ± 0.35
Organ failure estimates	1.08 ± 1.11
Outcome	

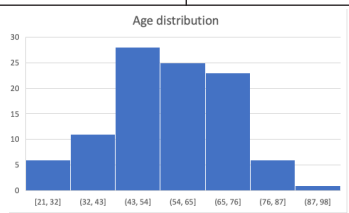


Figure 1 - Age distribution in patients with Sepis / septic shock

Research question 1 - Is there a direct correlation between Procalcitonin and outcome?

To test whether there was significant difference in Procalcitonin with respect to final outcome; t test for two independent samples is used.

Group Statistics

	FINAL OUTCOME	N	Mean	Std. Deviation	Std. Error Mean
PROCALCITONIN	DEATH	25	2.7116	1.82667	.36533
	DISCHARGED	75	.7996	.68459	.07905

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means		
		F	Sig.	t	df	P value (2-tailed)
PROCALCITONIN	Equal variances assumed	24.391	.000	7.651	98	.000
	Equal variances not assumed			5.115	26.281	.000

Summary: Since p value < 0.05, the level of significance; Procalcitonin differs significantly with respect to outcome. The mean values suggest that Procalcitonin is higher for the patients who died than that for patients who were discharged.

Research question 2 - Is there a direct correlation between Procalcitonin and Duration of ICU stay?

The Pearson's correlation coefficient between Procalcitonin & Duration of ICU stay is as given below & its significance is tested by t test.

PROCALCITONIN		
LENGTH OF ICU STAY	Pearson Correlation	.163
	p value (2-tailed)	.106
	N	100
*. Correlation is significant at the 0.05 level (2-tailed).		
**. Correlation is significant at the 0.01 level (2-tailed).		

Summary: Since p value > 0.05, the level of significance; the correlation between Procalcitonin & Duration of ICU stay is not significant.

Summary of results –

Our study showed that patients with a higher baseline value of serum procalcitonin had higher rate of in-hospital mortality (SD – 1.8 vs SD - 0.68, 2-tailed P<0.001). However, no statistically significant association was noted between baseline PCT and duration of ICU stay.

Discussion

The ability of serum procalcitonin at being able to predict mortality is a matter of controversy in modern critical care medicine. In the past decade there have been several studies on the subject, with no clear consensus reached. We explore both sides of the story in the following paragraphs. The authors realize that these studies may not be comparable head to head, however, serve to reflect the conceptually dubious nature of the findings on the subject.

In 2019 Akagi et al (9) suggested that procalcitonin was not independent predictor of 30-day mortality, although they did find a correlation between procalcitonin levels and severity of pneumonia. Andriolo et al (10) were similarly unable to correlate PCT levels with overall mortality. Khanna et al attempted to summarize various organ failure scores and PCT

levels to predict mortality in patients with acute pancreatitis (11).

The evidence to the contrary is equally overwhelming. Chiwakata et al demonstrated a statistically significant relationship between PCT and mortality in patients with Plasmodium falciparum malaria (12).Cotoi et al demonstrated a relationship between PCT levels and all cause mortality in patients with a previously diagnosed condition (13). Gul et al demonstrated an association, but not a direct correlation between procalcitonin levels and mortality in Crimean Congo Hemorrhagic fever (14). This study was unique in being to associate a viral infection with serum procalcitonin levels. Kenzaka et al demonstrated a significant correlation between PCT levels and mortality (15). Their study was also able to comment on the predictive ability of PCT.

Hanah Kim et al opined that a multi-marker approach to predict mortality in sepsis which included PCT, presepsin, and galectin 3 may be used to predict mortality in sepsis (16). Matsumura et al definitively stated that mortality in patients with higher PCT levels and that it was able to predict post ICU discharge mortality as well (17). John Victor Peter et al were able to correlate the levels of increased mortality in patients with scrub typhus infection and in those who would need ICU admission(18). Pierrali et al were able to demonstrate the rise of PCT in the first 72 hours and all cause mortality in patients with sepsis (8).

CONCLUSION

The predictive value of serum PCT, for mortality has been a matter of debate and controversy with compelling evidence to both sides of the story available in contemporary literature. Our study re-enforces the dictum of early diagnosis and treatment of sepsis in conjunction with the judicious use of serum procalcitonin. On the horizon, the authors see a plethora of newer biomarkers (SUPAR and sTREM-1) which may be used standalone or in combination to improve outcomes.

References:

1. Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: The evolution in definition, pathophysiology, and management. SAGE Open Med. 2019;7:2050312119835043.
2. Bracht H, Hafner S, Weiss M. [Sepsis Update: Definition and Epidemiology]. Anasthesiol Intensivmed Notfallmed Schmerzther. 2019;54(1):10-20.
3. Sinha S, Ray B. Sepsis-3: How useful is the new definition? J Anaesthesiol Clin Pharmacol. 2018;34(4):542-3.
4. de Jager CP, de Wit NC, Weers-Pothoff G, van der Poll T, Wever PC. Procalcitonin kinetics in Legionella pneumophila pneumonia. Clin Microbiol Infect. 2009;15(11):1020-5.
5. Lipinska-Gediga M, Mierzchala-Pasierb M, Durek G. Procalcitonin kinetics - prognostic and diagnostic significance in septic patients. Arch Med Sci. 2016;12(1):112-9.
6. Shi Y, Xu YC, Rui X, Zhang HM, Wang Y, Du W. Procalcitonin kinetics and nosocomial pneumonia in older patients. Respir Care. 2014;59(8):1258-66.
7. Poddar B, Gurjar M, Singh S, Aggarwal A, Singh R, Azim A, et al. Procalcitonin kinetics as a prognostic marker in severe sepsis/septic shock. Indian J Crit Care Med. 2015;19(3):140-6.
8. Pieralli F, Vannucchi V, Mancini A, Antonielli E, Luise F, Sammicheli L, et al. Procalcitonin Kinetics in the First 72 Hours Predicts 30-Day Mortality in Severely Ill Septic Patients Admitted to an Intermediate Care Unit. J Clin Med Res. 2015;7(9):706-13.
9. Akagi T, Nagata N, Miyazaki H, Harada T, Takeda S, Yoshida Y, et al. Procalcitonin is not an independent predictor of 30-day mortality, albeit predicts pneumonia severity in patients with pneumonia acquired outside the hospital. BMC Geriatr. 2019;19(1):3.
10. Andriolo BN, Andriolo RB, Salomao R, Atallah AN. Effectiveness and safety of procalcitonin evaluation for reducing mortality in adults with sepsis, severe sepsis or septic shock. Cochrane Database Syst Rev. 2017;1:CD010959.
11. Khanna AK, Meher S, Prakash S, Tiwary SK, Singh U, Srivastava A, et al. Comparison of Ranson, Glasgow, MOSS, SIRS, BISAP, APACHE-II, CTSI Scores, IL-6, CRP, and Procalcitonin in Predicting Severity, Organ Failure, Pancreatic Necrosis, and Mortality in Acute Pancreatitis. HPB Surg. 2013;2013:367581.
12. Chiwakata CB, Manegold C, Bonicke L, Waase I, Julch C, Dietrich M. Procalcitonin as a parameter of disease severity and risk of mortality in patients with Plasmodium falciparum malaria. J Infect Dis. 2001;183(7):1161-4.
13. Cotoi OS, Manjer J, Hedblad B, Engstrom G, Melander O, Schiopu A. Plasma procalcitonin is associated with all-cause and cancer mortality in apparently healthy men: a prospective population-based study. BMC Med. 2013;11:180.
14. Gul S, Ozturk DB, Kisa U, Kacmaz B, Yesilyurt M. Procalcitonin Level and Its Predictive Effect on Mortality in Crimean-Congo Hemorrhagic Fever Patients. Jpn J Infect Dis. 2015;68(6):511-3.
15. Kenzaka T, Okayama M, Kuroki S, Fukui M, Yahata S, Hayashi H, et al. Use of a semiquantitative procalcitonin kit for evaluating severity and predicting mortality in patients with sepsis. Int J Gen Med. 2012;5:483-8.
16. Kim H, Hur M, Moon HW, Yun YM, Di Somma S, Network G. Multi-marker approach using procalcitonin, presepsin, galectin-3, and soluble suppression of tumorigenicity 2 for the prediction of mortality in sepsis. Ann Intensive Care. 2017;7(1):27.
17. Matsumura Y, Nakada TA, Abe R, Oshima T, Oda S. Serum procalcitonin level and SOFA score at discharge from the intensive care unit predict post-intensive care unit mortality: a prospective study. PLoS One. 2014;9(12):e114007.
18. Peter JV, Karthik G, Ramakrishna K, Griffith MF, Jude Prakash JA, Job V, et al. Elevated procalcitonin is associated with increased mortality in patients with scrub typhus infection needing intensive care admission. Indian J Crit Care Med. 2013;17(3):174-7.